> [T]here is absolutely no evidence of record or any line or reasoning that would support a conclusion that the vascular IBP-like growth factor (VIGF) of the instant application can be used for wound healing and associated therapies, for enhancement of growth of vascular smooth muscle and endothelial cells, and therapeutically in ischemic tissues and for coronary stenosis (see page 19 of the specification) for the reasons provided above. There is no evidence of record that the instant invention is related (i.e., no reasonable correlation) to any of the diseases indicated (i.e., muscle wasting, osteoporosis, implant fixation, tissue regeneration, etc.), and therefore, there is no evidence to support use of the claimed invention as a therapeutic agent for treating any of these conditions.

See, Paper No. 31, Page 5, Paragraph 6.

Applicants respectfully disagree and traverse.

As detailed in their response of July 16, 2001, Applicants have set forth in the specification statements that clearly and fully describe the function of VIGF and explain why Applicants believe the invention is useful. For example, the specification explicitly teaches that VIGF has use, for example, to proliferate vascular smooth muscle and endothelial cells (*see, e.g.*, the instant specification at page 4, lines 11-15; and page 20, line 24 through page 21, line 6); as a tumor diagnostic (*see, e.g.*, the instant specification at page 26, second full paragraph; and page 27, final paragraph through the top of page 28); and/or to accelerate the mitogenic activity of other growth factors (*see, e.g.*, the instant specification at page 24, first paragraph). Thus, the specification clearly teaches specific, substantial and credible assertions of utility of the disclosed polynucleotides (and the encoded polypeptides) as a tumor diagnostic, and/or as involved in the enhancement of growth of vascular smooth muscle and endothelial cells associated with the stimulation of angiogenesis and tissue regeneration (*see, e.g.*, page 19, first and second full paragraph). The biological role and significance of VIGF polynucleotides (and the encoded polypeptides), as well as its specific and substantial utility, are clearly taught by the specification as originally filed. Applicants assert that such characterization is sufficient on its own to constitute a showing of utility.

Furthermore, Bechard et al., have further analyzed the VIGF protein which they call Endothelial-cell-specific molecule 1 (ESM-1), as cited in Applicants' response filed October 25, 2001. In addition, Bechard et al., have determined that ESM-1 (now referred to by Bechard et al. with the proposed name of "Endocan") regulates Hepatocyte growth factor/scatter factor (HGS/SF) -mediated mitogenic activity and may support the function of HGF/SF not only in embryogenesis and tissue repair after injury but also in tumor progression (*see*, Bechard et al., J. Biological Chem. 276:48341-48349 (2001) at page 48341,

end of the abstract, provided in the Supplemental Information Disclosure Statement as reference AI). Bechard et al., states that

> HGF/SF also increases angiogen sis, mainly when combined with vascular endothelial growth factor. Endocan may be implicated in these phenomena of dysregulated HGF/SF motogenic, mitogenic, and angiogenic activities. Supporting this idea, the concentration of endocan was found to be elevated in the sera of patients with lung cancer (data not shown).

(*see,* Bechard et al., *supra* at page 48348, second column).

Bechard et al. further teach:

> The fact that endocan is specifically secreted by endothelial cells suggests that it may represent a novel factor able to regulate the functions of HGF/SF, and perhaps other GAG-binding regulatory proteins, in areas of embryonic development, tissue regeneration, or tumor progression and that it may be particularly important in the context of emerging therapeutic applications of HGF/SF

(*see,* Bechard et al., *supra* at page 48349, first column). Thus, as asserted by Applicants, VIGF is useful as a tumor diagnostic, and to enhance the proliferation of endothelial cells associated with tissue regeneration and angiogenesis.

Applicants submit that the above asserted utilities for VIGF are specific (the vast majority of proteins are not useful as a tumor diagnostic, and do not enhance growth of vascular smooth muscle and endothelial cells leading to stimulation of angiogenesis or tissue regeneration) and substantial ("the general rule [is] that the treatments of specific diseases or conditions meet the criteria of 35 U.S.C. § 101." (Revised Interim Utility Guidelines Training Materials, p. 6)). In addition, Applicants submit that these utilities are credible.

With regard to these asserted therapeutic activities, Applicants note that there is no need to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty or provide actual evidence of success in treating humans where such a utility is asserted. M.P.E.P. § 2107.02 (I) at 2100-[33-34]. All that is required of Applicants is that there be a reasonable correlation between the biological activity and the asserted utility. *See, Nelson v. Bowler,* 626 F.2d 853, 857 (C.C P A. 1980). Moreover, "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *In re Brana, 51* F.3d *1560, 1568* (Fed. Cir. 1995) (emphasis added)

Even assuming, *arguendo*, the Examiner has established a *prima facie* showing that the claimed invention lacks utility, Applicants respectfully submit that they have rebutted the Examiner's showing by proffering sufficient evidence that one skilled in the art would conclude that the asserted utilities are more likely than not true. Applicants have directed the Examiner to the specification where clear and specific assertions are made of VIGF biological and therapeutic activity and provided experimental evidence confirming the asserted utilities.

In view of the above, Applicants submit that the asserted utilities of the invention meet the statutory requirement set forth in 35 U.S.C. § 101. The Examiner has failed to establish and maintain grounds as to why a rejection for lack of utility is proper. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Rejections Under 35 U.S.C. § 112

A. The Examiner has also rejected claims 54-67, 75-92, 102-107, and 115-119, and 122-175 under 35 U.S.C. § 112, first paragraph, as allegedly failing to adequately teach how to use the instant invention for the reasons given with regard to the rejection of these claims under 35 U.S.C. § 101.

Applicants respectfully disagree and traverse.

For the reasons discussed above in response to the rejection under 35 U.S.C. § 101, Applicants submit that the claimed invention is supported by a specific and substantial or well-established utility, for example, to enhance the growth of vascular smooth muscle and endothelial cells leading to the stimulation of angiogenesis (*see*, e.g., page 19, lines 7-9, and Example 5). Moreover, this immediate and specific utility is explicitly taught in the specification as filed. The Examiner "should not impose a 35 U S.C. § 112, first paragraph, rejection grounded on a "lack of utility" basis unless a 35 U.S C. § 101 rejection is proper." M.P E.P. § 2107(IV) at 2100-28 (Rev.1, Feb. 2000). Therefore, since the claimed invention complies with the utility requirement of 35 U.S.C § 101, the rejection of claims under 35 U S.C. § 112, first paragraph, based on lack of utility of the claimed invention, should be withdrawn.

B. The Examiner rejects claim 176 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

More particularly, the Examiner alleges:

> Claim 176 is directed to a polynucleotide encoding a polypeptide which "consists of amino acids +1 to +163 of SEQ ID NO:2, in which 1 or more amino acid residues are substituted, deleted or added, in any combination". These two recitations are inconsistent with one another, because if the polypeptide is to consist of a particular sequence of amino acids, it is not clear how it can also have modifications of that sequence. Furthermore, the claim encompasses modification of up to every amino acid in the sequence, therefore, it would no longer "consist" of the sequence of SEQ ID NO:2 Therefore, the claims are completely confusion in that it is not clear if the polypeptide consists of a particular sequence, or if it does not consist of that sequence.

See, Paper No. 31, Page 6, Paragraph 8.

Applicants respectfully disagree with the Examiner. Nevertheless, solely in the interest of facilitating prosecution, Applicants have cancelled claim 176 without prejudice or disclaimer, thereby mooting the rejection. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Rejections Under 35 U.S.C. § 102(b)

The Examiner rejects claim 176 under 35 U.S.C. § 102(b), as allegedly being anticipated by Bradham et al. (J. Cell Biol. 114(6): 1285-1294, 1991).

More specifically the Examiner contends:

> Claim 176 encompasses polynucleotides encoding polypeptides which have any number of amino acid substitutions, deletions, additions, or combinations thereof. Therefore, the claim encompasses any isolated polynucleotide in existence. Therefore, the polynucleotide of Bradham et al anticipates the instant claim (see Figure 8A).

See, Paper No. 31, Page 7, Paragraph 10.

Applicants respectfully disagree with the Examiner. Nevertheless, solely in the interest of expediting prosecution, Applicants have cancelled claim 176 without prejudice or disclaimer, thereby mooting the rejection. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Conclusion

If there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Dated: December 19, 2001

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